

# BEST AVAILABLE COPY

**PCT**

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>5</sup> :  A01N 45/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 92/00010  (43) International Publication Date: 9 January 1992 (09.01.92)</p>
<p>(21) International Application Number: PCT/US91/04508 (22) International Filing Date: 21 June 1991 (21.06.91) (30) Priority data: 544,709 27 June 1990 (27.06.90) US (71) Applicant: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Patents - U.S., 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406 (US). (72) Inventor: RANDALL, Keith, Johnson ; 71 Llanfair Circle, Ardmore, PA 19003 (US). (74) Agents: DUSTMAN, Wayne, J. et al.; SmithKline Bee- cham Corporation, Corporate Patents - U.S. (UW2220), 709 Swedeland Road, King of Prussia, PA 19406 (US).</p>	<p>(81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (Euro- pean patent).  Published With international search report.</p>	
<p>(54) Title: METHOD OF TREATING HUMAN PROSTATIC ADENOCARCINOMA</p> <p>(57) Abstract</p> <p>Invented is a method of treating human prostatic adenocarcinoma by employing a steroid 5-<math>\alpha</math>-reductase inhibiting com- pound or a combination of steroid 5-<math>\alpha</math>-reductase inhibiting compounds.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

5

10

- 1 -

METHOD OF TREATING HUMAN PROSTATIC ADENOCARCINOMA

15        This invention relates to a new method of treating  
human prostatic adenocarcinoma by employing a steroid 5- $\alpha$ -  
reductase inhibiting compound. Advantageously the method of  
this invention employs 17 $\beta$ -(N-t-butylcarboxamide)-androst-  
3,5-diene-3-carboxylic acid in the symptomatic relief of  
20    human prostatic adenocarcinoma.

BACKGROUND OF THE INVENTION

25        The class of steroidal hormones known as androgens is  
responsible for the physical characteristics that  
differentiate males from females. Of the several organs  
that produce androgens, the testes produce these hormones in  
the greatest amounts. Centers in the brain exert primary  
30    control over the level of androgen production. Numerous  
physical manifestations and disease states result when  
ineffective production control results in excessive androgen  
hormone production. For example, acne vulgaris, seborrhea,  
female hirsutism, and benign prostatic hypertrophy are  
35    correlated with elevated androgen levels. Additionally, the  
incidence of male pattern baldness has been associated with  
high androgen levels.

Testosterone is the principal androgen secreted by the testes and is the primary androgenic steroid in the plasma of males. It now is known that 5- $\alpha$ -reduced androgens are active hormones in some tissues such as the prostate and sebaceous gland. Circulating testosterone thus serves as a prohormone for dihydrotestosterone (DHT), its 5- $\alpha$ -reduced analogue in these tissues but not in others such as muscle and testis. Steroid 5- $\alpha$ -reductase is a NADPH-dependent enzyme that converts testosterone to DHT. The importance of this enzyme in male development was dramatically underscored by discovery of a genetic steroid 5- $\alpha$ -reductase deficiency in male pseudohermaphrodites. Imperato-McGinley, J., et al., (1979), J. Steroid Biochem. 11:637-648.

Recognition of the importance of elevated DHT levels in various disease states has stimulated many efforts to synthesize inhibitors of this enzyme.

The first inhibitor described was 4-androsten-3-one-17 $\beta$ -carboxylic acid by Hisa and Voight in 1973. J. Invest. Dermat. 62:224-227. (4R)-5,10-seco-19-norpregna-4,5-diene-3,10,20-triene was the next inhibitor to be described and also has found utility as an affinity label for 5- $\alpha$ -reductase. Robaire, B., et al., (1977), J. Steroid Biochem. 8:307-310. (5 $\alpha$ ,20-R)-4-diazo-21-hydroxy-20-methylpregnan-3-one has been reported as a potent, time-dependent inhibitor of steroid 5- $\alpha$ -reductase. Blohm, T.R., et al., (1980), Biochem. Biophys. Res. Comm. 95:273-280; United States Patent 4,317,817, March 2, 1982. 17 $\beta$ -N,N-diethylcarbamoyl-4-methyl-4-aza-5- $\alpha$ -androstan-3-one is exemplary of a group of 4-aza steroid inhibitors of steroid 5- $\alpha$ -reductase described in United States Patent 4,377,584 which issued March 22, 1983, and in Liang, T., et al., (1983), J. Steroid Biochem. 19, 385-390. 17 $\alpha$ -acetoxy-6-methylenepregn-4-ene-3,20-dione also has been shown to be a time-dependent inactivator of steroid 5- $\alpha$ -reductase. Petrow, V., et al., (1981), Steroids 38:121-140.

Other steroid 5- $\alpha$ -reductase inhibitors also have been described. United States Patent 4,361,578 which issued June 2, 1986, describes a class of homosteroid enzyme inhibitors. 5 United States Patent 4,191,759 discloses amides of 17 $\beta$ -carboxy-4-androsten-3-one that are active as steroid 5- $\alpha$ -reductase inhibitors. Japanese Patents J60146855-A and J60116657-A disclose various aniline derivatives having numerous activities including 5- $\alpha$ -reductase inhibiting 10 activity. Japanese Patent I60142941-A discloses phenyl-substituted ketones having 5- $\alpha$ -reductase inhibiting activity and European Patent EP173516-A discloses various phenyl-substituted amides having similar activity. Shiseido referenced terpene derivatives that are active inhibitors of 15 steroid 5- $\alpha$ -reductase. Japanese Patent J59053417-A.

It has been postulated but never proven that the inhibition of steroid 5- $\alpha$ -reductase would result in a therapeutic effect on prostatic adenocarcinoma in mammals, 20 Novel Approaches to Cancer Chemotherapy, Pub: Academic Press, Inc. (1984) Ch.8 V. Petrow and G. Padilla 5- $\alpha$ -reductase: A target enzyme for Prostatic Cancer, however, contrary evidence has also been published, Liang, t., et al., (1985), Endocrinology 117, No. 2: 571-579.

25 It has now been discovered that steroid 5- $\alpha$ -reductase inhibitors do have a therapeutic effect on human prostatic adenocarcinoma.

### 30 SUMMARY OF THE INVENTION

The present invention resides in the discovery that steroid 5- $\alpha$ -reductase inhibiting compounds have a therapeutic effect on human prostatic adenocarcinoma.

35 Included in the present invention are combinations of steroid 5- $\alpha$ -reductase inhibitors and pharmaceutical

compositions comprising a pharmaceutical carrier and a compound or a combination of compounds useful in the method of the invention.

5

#### DESCRIPTION OF THE INVENTION

An inhibitor of steroid 5- $\alpha$ -reductase or a combination of inhibitors of steroid 5- $\alpha$ -reductase are used in a pharmaceutical composition to treat human prostatic  
10 adenocarcinoma.

Also included are derivatives of these compounds which may either give rise to the parent compounds in vivo or be useful themselves, such as pharmaceutically acceptable addition salts. Salts of these compounds containing a basic  
15 group are formed with organic or inorganic acids in the presence of a basic compound by methods known to the art. For example, the compound is reacted with an inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing the solvent or in an  
20 aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Exemplary of the acid addition salts which are included in this invention are maleate, fumarate, lactate, oxalate,  
25 methane sulfonate, ethanesulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate, phosphate and nitrate salts. Pharmaceutically acceptable base addition salts of compounds of the invention containing an acidic group are prepared by known methods from organic  
30 and inorganic bases include nontoxic alkali metal and alkaline earth bases, for example, calcium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases such as triethylamine, butylamine, piperazine, and (trihydroxymethyl)methylamine. Prodrug derivatives  
35 include O-esters, especially the tri-O-lower alkanol ester having from 2-8 carbon atoms in each alkanoyl group; O-

methly ethers or sulfate esters. Separated R and S stereoisomers are also useful.

- Compounds that are considered to be steroid 5- $\alpha$ -  
5 reductase inhibitors include:  
17B-(N-t-butylcarboxamide)-5- $\alpha$ -androst-1-ene-4-aza-3-one,  
(20R)-hydroxymethyl-4-methyl-4-aza-5- $\alpha$ -pregnane-3-one,  
10 17B-(N,N-diisopropylcarboxamide)-5- $\alpha$ -8(14)-androst-4-methyl-4-aza-3-one,  
17B-(N-t-butylcarboxamide)-5- $\alpha$ -8(14)-androst-4-methyl-4-aza-3-one,  
17B-(N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -androst-  
15 3-ene,  
17B-(N-t-butylcarboxamide)-3-nitro-5- $\alpha$ -androst-3-ene,  
17B-(N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -androst-2-ene,  
17B-(N-t-butylcarboxamide)-androst-3,5-diene-3-  
20 carboxylic acid or a salt thereof,  
17B-(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof,  
17B-(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof,  
25 17B-(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof,  
17B-(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-triene-3-sulfonic acid or a salt thereof,  
20- $\alpha$ -(hydroxymethyl)-A-nor-5- $\alpha$ -pregn-1-ene-2-  
30 carboxylic acid or a salt thereof,  
17B-(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-sulfonic acid or a salt thereof,  
17B-(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-triene-3-phosphonic acid or a salt thereof,  
35 17B-(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-phosphonic acid or a salt thereof,

- 17 $\beta$ -(N,N-diisopropylcarboxamide)-estra-1,3,5(10-triene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-phosphinic acid or a salt thereof,  
5 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-phosphonic acid or a salt thereof,  
10 17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphonic acid or a salt thereof,  
(E)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-ene-3-ylidene-acetic acid or a salt thereof,  
15 17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-acetic acid or a salt thereof,  
(Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-ene-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-2-ene-3-acetic acid or a salt thereof,  
20 (Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ene-3-acetic acid or a salt thereof, and  
25 17 $\beta$ -(N-t-butylcarboxamide)-5 $\alpha$ -androst-2-ene-3-acetic acid or a salt thereof.

Persons skilled in the art can readily determine if a compound is a steroid 5- $\alpha$ -reductase inhibitor by known  
30 methods. All such compounds are included within the scope of this invention.

Because steroid 5- $\alpha$ -reductase inhibitors decrease the size of human prostate tumors, they have therapeutic utility  
35 in treating human prostate adenocarcinoma.



17B-(N-t-butylcarboxamide)-androst-3,5-diene- 3-carboxylic acid (compound A) was tested for its in vivo potency in treating human prostatic cancer.

5        To perform experiments on the human prostatic cancer model, a total of 80 nude mice were used. Each of these animals was inoculated in the flank with PC-82 human prostatic cancer and allowed to go untreated until the tumors were approx. 0.5 cc<sup>3</sup> in size (approx. 50 days after  
10        inoculation). After this period, 60 of the 80 animals were castrated. A 1 cm long testosterone filled silastic capsule was implanted subcutaneously in the flank of 20 of the castrated animals and a 2 cm long dihydrotestosterone filled  
15        silastic capsule was implanted subcutaneously in the flank of 20 of the castrated animals. The 80 animals were set up in 8 groups as follows:

GROUP 1 - intact rats fed twice a day with vehicle alone (intact controls).

20

GROUP 2 - castrated rats fed twice a day with vehicle and not implanted with testosterone or dihydrotestosterone capsule (castrate controls).

25        GROUP 3 - intact rats fed compound (A) (BID) 50 mg/kg.

GROUP 4 - castrated rats fed compound (A) (BID) 50 mg/kg and not implanted with testosterone or dihydrotestosterone capsule.

30

GROUP 5 - castrated rats fed twice a day with vehicle and implanted with testosterone capsule.

35        GROUP 6 - castrated rats fed compound (A) (BID) 50 mg/kg and implanted with testosterone capsule.

GROUP 7 - castrated rats fed twice a day with vehicle and implanted with dihydrotestosterone capsule.

5 GROUP 8 - castrated rats fed compound (A) (BID) 50 mg/kg and implanted with dihydrotestosterone capsule.

The animals were administered the 5- $\alpha$ -reductase inhibiting compound twice a day (BID) for 5 consecutive weeks. The test compound was dissolved in propylene glycol and diluted in water. Tumor volume was measured by caliper  
10 twice a week, At the end of the treatment period blood was collected from the animals and they were sacrificed, the ventral prostates were excised and weighed and the serum androgen levels were determined by known methods. Ewing at  
15 al Endocrinology 113:2004-2009, 1983.

The nude mice treated with compound (A) realized a significant decrease in the size of the implanted PC-82 human prostatic cancer, in addition to other therapeutic  
20 effects normally associated with inhibitors of steroid 5- $\alpha$ -reductase. Thus, the administration of a steroid 5- $\alpha$ -reductase inhibiting compound results in a therapeutic effect on human prostatic adenocarcinoma.

25 The claimed compounds and combinations are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose,  
30 talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with  
35 a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will

be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

5       The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the  
10       desired oral or parenteral products.

Doses of the present compounds and combinations in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of  
15       0.1 - 1000 mg/kg of each active compound, preferably 1-100 mg/kg. The selected dose is administered to a human patient in need of treatment for prostatic adenocarcinoma from 1-6 times daily, orally, by injection or continuously by infusion. Oral dosage units for human administration  
20       preferably contain from 1 to 500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at higher dosages, however, also can be used when safe and convenient for the patient.

25       The method of this invention of treating human prostatic adenocarcinoma comprises administering to a subject in need thereof an effective amount of a steroid 5- $\alpha$ -reductase inhibiting compound.

30       Following are the results of testing the compounds of this invention:

TABLE I

35       The effect of 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid (compound A) on inhibiting the growth of PC-82 Human Prostatic adenocarcinoma.

TABLE I

Group No.	Treatment (N=6 rats/group)	0	1	2	3	4	5
Tumor volume (cm <sup>3</sup> ) at identical weeks of treatment							
Group 1	Intact Control	0.39±0.06 (100)	0.71±0.34 (120)	0.87±0.19 (147)	1.18±0.20 (200)	1.24±0.18 (217)	1.55±0.31 (263)
Group 2	Castrated	0.64±0.07 (100)	0.31±0.11 (88)	0.44±0.09 (69)	0.43±0.15 (64)	0.23±0.16 (39)	0.27±0.10 (42)
Group 3	Intact + compound A	0.30±0.04 (100)	0.43±0.05** (90)	0.40±0.06* (80)	0.38±0.07* (76)	0.36±0.03* (72)	0.34±0.06** (66)
Group 4	Castrated + compound A	0.62±0.10 (100)	0.31±0.11 - (82)	0.33±0.09 (56)	0.30±0.10 (44)	0.28±0.07 (43)	0.29±0.03 (47)
Group 5	Castrated + testosterone implant	0.48±0.12 (106)	0.69±0.07 (163)	0.78±0.14 (182)	1.12±0.15 (233)	1.32±0.19 (273)	1.60±0.43 (333)
Group 6	Castrated + testosterone implant + compound A	0.33±0.17 (100)	0.32±0.10 (93)	0.45±0.09 (82)	0.40±0.11 (73)	0.33±0.17 (64)	0.38±0.13 (69)
Group 7	Castrated + DHT implant	0.62±0.10 (100)	0.74±0.07 (119)	0.93±0.12 (150)	1.74±0.22 (200)	1.43±0.31 (239)	1.78±0.32 (287)
Group 8	Castrated + DHT implant + compound A	0.49±0.09 (100)	0.63±0.11 (133)	0.87±0.13 (177)	1.05±0.19 (214)	1.32±0.35 (269)	1.72±0.38 (351)

\* Statistically significant

Values in parentheses are the relative percentages versus the starting values for each group at time 0.

The data in the above table demonstrates the therapeutic effect of steroid 5- $\alpha$ -reductase inhibitors on human prostatic adenocarcinoma.

5       The following examples illustrate preparation of the claimed pharmaceutical compositions containing steroid 5- $\alpha$ -reductase inhibitors. The examples are not intended to limit the scope of the invention as defined herein above and as claimed below.

10

EXAMPLE 1

      An oral dosage form for administering the claimed compounds is produced by screening, mixing and filling into  
15   hard gelatin capsules the ingredients in the proportions shown in table II below.

TABLE II

20	<u>INGREDIENTS</u>	<u>AMOUNTS</u>
	17 $\beta$ -(N-t-butylcarboxamide)-androst-	100 mg
	3,5-diene-3-carboxylic acid	
	Magnesium stearate	5 mg
	Lactose	75 mg

EXAMPLE II

25       The sucrose, calcium sulfate dihydrate and claimed compound shown in Table III below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a  
30   tablet.

TABLE III

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
17 $\beta$ -(N-t-butylcarboxamide)- androst-3,5-diene-3-carboxylic acid	100 mg
Calcium sulfate dihydrate	150 mg
Sucrose	20 mg
Starch	10 mg
Talc	5 mg
Stearic Acid	3mg

5

EXAMPLE III

17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid (1.0g) is dissolved in 20g of soybean oil and emulsified by mixing with 1.2g of egg phospholipid and enough water to bring the final volume to 100 ml. The formed interlipid formulation is suitable for intravenous administration.

15 While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming with the scope of the following claims is reserved.

20

What is claimed is:

1. A method of treating human prostatic adenocarcinoma which comprises administering to a subject in need thereof an effective amount of a steroid 5- $\alpha$ -reductase inhibiting compound.  
5
2. The method of claim 1 which comprises administering a dosage unit containing from about 0.1 mg to about 1000 mg of said steroid 5- $\alpha$ -reductase inhibiting compound.  
10
3. The method of claim 1 in which the steroid 5- $\alpha$ -reductase inhibiting compound is 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof.  
15
4. The method of claim 1 in which the steroid 5- $\alpha$ -reductase inhibiting compound is:  
20  
17 $\beta$ -(N-t-butylcarboxamide)-5- $\alpha$ -androst-1-ene-4-aza-3-one,  
(20R)-hydroxymethyl-4-methyl-4-aza-5- $\alpha$ -pregnane-3-one,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-5- $\alpha$ -8(14)-androst-4-methyl-4-aza-3-one,  
25 17 $\beta$ -(N-t-butylcarboxamide)-5- $\alpha$ -8(14)-androst-4-methyl-4-aza-3-one,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -androst-3-ene,  
30 17 $\beta$ -(N-t-butylcarboxamide)-3-nitro-5- $\alpha$ -androst-3-ene,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -androst-2-ene,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof,  
35 17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof,

- 17 $\beta$ -(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-  
triene-3-carboxylic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-carboxylic acid or a salt thereof,  
5 17 $\beta$ -(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-  
triene-3-sulfonic acid or a salt thereof,  
20- $\alpha$ -(hydroxymethyl)- $\Delta$ -nor-5- $\alpha$ -pregn-1-ene-2-  
carboxylic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
10 3-sulfonic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)estra-1,3,5(10)-  
triene-3-phosphonic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-phosphonic acid or a salt thereof,  
15 17 $\beta$ -(N,N-diisopropylcarboxamide)estra-1,3,5(10)-  
triene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-  
20 phosphinic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-  
diene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-  
phosphonic acid or a salt thereof,  
25 17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-  
diene-3-phosphonic acid or a salt thereof,  
(E)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-  
ene-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5  
30 -diene-3-acetic acid or a salt thereof,  
(Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-  
ene-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-2-  
ene-3-acetic acid or a salt thereof,  
35 (Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-  
3-ylidene-acetic acid or a salt thereof,



17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ene-3-acetic acid or a salt thereof, or  
17 $\beta$ -(N-t-butylcarboxamide)-5 $\alpha$ -androst-2-ene-3-acetic acid or a salt thereof.

5

5. The method of Claim 1 in which the steroid 5- $\alpha$ -reductase inhibiting compound is 17 $\beta$ -(N-t-butylcarboxamide)-5- $\alpha$ -androst-1-ene-4-aza-3-one.

10

6. The method of Claim 1 in which the steroid 5- $\alpha$ -reductase inhibiting compound is 17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof.

7. The method of treating human prostatic  
15 adenocarcinoma which comprises administering to a subject in need thereof an effective amount of a combination of steroid 5- $\alpha$ -reductase inhibiting compounds.

8. The method according to claim 1 or claim 7 wherein  
20 the compound is administered parenterally.

9. The method according to claim 1 or claim 7 wherein the compound is administered orally.

25 10. Use of a steroid 5- $\alpha$ -reductase inhibiting compound in the manufacture of a medicament for use in the treatment of human prostatic adenocarcinoma.

11. The use according to claim 10 which comprises  
30 administering a dosage unit containing from about 0.1 mg to about 1000 mg of said steroid 5- $\alpha$ -reductase inhibiting compound.

12. The use according to claim 10 wherein the compound  
35 is 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof.

13. The use according to claim 10 wherein the compound is:

- 17B- (N-t-butylcarboxamide)-5- $\alpha$ -androst-1-ene-4-  
aza-3-one,  
5 (20R)-hydroxymethyl-4-methyl-4-aza-5- $\alpha$ -pregnane-  
3-one,  
17B- (N,N-diisopropylcarboxamide)-5- $\alpha$ -8(14)-  
androst-4-methyl-4-aza-3-one,  
17B- (N-t-butylcarboxamide)-5- $\alpha$ -8(14)-androst-4-  
10 methyl-4-aza-3-one,  
17B- (N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -  
androst-3-ene,  
17B- (N-t-butylcarboxamide)-3-nitro-5- $\alpha$ -androst-3-  
ene,  
15 17B- (N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -  
androst-2-ene,  
17B- (N-t-butylcarboxamide)-androst-3,5-diene-3-  
carboxylic acid or a salt thereof,  
17B- (N,N-diisopropylcarboxamide)-androst-3,5-  
20 diene-3-carboxylic acid or a salt thereof,  
17B- (N,N-diisopropylcarboxamide)-estra-1,3,5(10)-  
triene-3-carboxylic acid or a salt thereof,  
17B- (N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-carboxylic acid or a salt thereof,  
25 17B- (N,N-diisopropylcarboxamide)-estra-1,3,5(10)-  
triene-3-sulfonic acid or a salt thereof,  
20- $\alpha$ -(hydroxymethyl)-A-nor-5- $\alpha$ -pregn-1-ene-2-  
carboxylic acid or a salt thereof,  
17B- (N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
30 3-sulfonic acid or a salt thereof,  
17B- (N,N-diisopropylcarboxamide)estra-1,3,5(10)-  
triene-3-phosphonic acid or a salt thereof,  
17B- (N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-phosphonic acid or a salt thereof,  
35 17B- (N,N-diisopropylcarboxamide)estra-1,3,5(10)-  
triene-3-phosphinic acid or a salt thereof,

- 17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-phosphinic acid or a salt thereof,  
5 17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-phosphonic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphonic acid or a salt thereof,  
10 (E)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-ene-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-acetic acid or a salt thereof,  
15 (Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-ene-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-2-ene-3-acetic acid or a salt thereof,  
(Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ylidene-acetic acid or a salt thereof,  
20 17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ene-3-acetic acid or a salt thereof, or  
17 $\beta$ -(N-t-butylcarboxamide)-5 $\alpha$ -androst-2-ene-3-acetic acid or a salt thereof.
- 25 14. The use according to claim 10 wherein the compound is 17 $\beta$ -(N-t-butylcarboxamide)-5- $\alpha$ -androst-1-ene-4-aza-3-one.
- 30 15. The use according to claim 10 wherein the compound is 17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof.
- 35 16. Use of a combination of steroid 5- $\alpha$ -reductase inhibiting compounds in the manufacture of a medicament for use in the treatment of human prostatic adenocarcinoma.

17. The use according to claim 10 or claim 16 wherein the medicament is adapted for parenteral administration.

18. The use according to claim 10 or claim 16 wherein  
5 the medicament is adapted for oral administration.

19. The pharmaceutical composition for use in the treatment of human prostatic adenocarcinoma comprising a steroid 5- $\alpha$ -reductase inhibiting compound and a  
10 pharmaceutically acceptable carrier.

20. The composition according to claim 19 wherein the compound administered is in a 0.1 mg to 1000 mg unit dose.

21. The composition according to claim 19 wherein the compound to be administered is 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof.

22. The composition according to claim 19 wherein the  
20 compound to be administered is:

17 $\beta$ -(N-t-butylcarboxamide)-5- $\alpha$ -androst-1-ene-4-aza-3-one,

(20R)-hydroxymethyl-4-methyl-4-aza-5- $\alpha$ -pregnane-3-one,

25 17 $\beta$ -(N,N-diisopropylcarboxamide)-5- $\alpha$ -8(14)-androst-4-methyl-4-aza-3-one,

17 $\beta$ -(N-t-butylcarboxamide)-5- $\alpha$ -8(14)-androst-4-methyl-4-aza-3-one,

30 17 $\beta$ -(N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -androst-3-ene,

17 $\beta$ -(N-t-butylcarboxamide)-3-nitro-5- $\alpha$ -androst-3-ene,

17 $\beta$ -(N,N-diisopropylcarboxamide)-3-nitro-5- $\alpha$ -androst-2-ene,

35 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-carboxylic acid or a salt thereof,

- 17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-  
diene-3-carboxylic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-  
triene-3-carboxylic acid or a salt thereof,  
5 17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-carboxylic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-estra-1,3,5(10)-  
triene-3-sulfonic acid or a salt thereof,  
20- $\alpha$ -(hydroxymethyl)-A-nor-5- $\alpha$ -pregn-1-ene-2-  
10 carboxylic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-sulfonic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)estra-1,3,5(10)-  
triene-3-phosphonic acid or a salt thereof,  
15 17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
3-phosphonic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)estra-1,3,5(10)-  
triene-3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-  
20 3-phosphinic acid or a salt thereof,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-  
phosphinic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-  
diene-3-phosphinic acid or a salt thereof,  
25 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-  
phosphonic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-  
diene-3-phosphonic acid or a salt thereof,  
(E)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-  
30 ene-3-ylidene-acetic acid or a salt thereof,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-3,5-  
-diene-3-acetic acid or a salt thereof,  
(Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-androst-4-  
ene-3-ylidene-acetic acid or a salt thereof,  
35 17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-2-  
ene-3-acetic acid or a salt thereof,

(Z)-17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ylidene-acetic acid or a salt thereof,

17 $\beta$ -(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ene-3-acetic acid or a salt thereof, or

5 17 $\beta$ -(N-t-butylcarboxamide)-5 $\alpha$ -androst-2-ene-3-acetic acid or a salt thereof.

23. The composition according to claim 19 wherein the compound to be administered is 17 $\beta$ -(N-t-butylcarboxamide)-5-  
10  $\alpha$ -androst-1-ene-4-aza-3-one.

24. The composition according to claim 19 wherein the compound to be administered is 17 $\beta$ -(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof.

15

25. A pharmaceutical composition for use in the treatment of human prostatic adenocarcinoma comprising a combination of steroid -5- $\alpha$ -reductase inhibiting compounds and a pharmaceutically acceptable carrier.

20

26. The composition according to claim 19 or claim 25 which is adapted for parenteral administration.

27. The composition according to claim 19 or claim 25  
25 which is adapted for oral administration.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04508

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(5): A01N 45/00		
U.S. CL. 514/169		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
U.S.	514/169, 172, 173, 177, 178, 182, 319, 428, 462, 510, 573	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT *</b>		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
X Y	"Retardation of Prostate Tumor Progression in the Noble Rat by 4-Methyl-4-aza-steroidal Inhibitors of 5 Alpha-Reductase", KADOHAMA ET AL., <u>Journal of the National Cancer Institute</u> ; 74(2), pages 475-486, (1985), ISSN 0027-8874	1, 19 1-9, 19-27
X Y	"Species Differences in Prostatic Steroid 5 Alpha-Reductases of Rat, Dog and Human", LIANG ET AL, <u>Endocrinology</u> , 117, No. 2, pages 571-579, 1985.	1, 19 1-9, 19-27
Y	EP, B, 0 004 949 (JOHNSON ET AL.) 21 SEPTEMBER 1983; See page 2	1-9, 19-27
Y	EP, A, 0 285 383 (RASMUSSEN ET AL.) 06 OCTOBER 1988 See Description of the Prior Art.	1-9, 19-27
<p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
30 JULY 1991	01 OCT 1991	
International Searching Authority	Signature of Authorized Officer	
ISA/US	Carlos Azpuru	

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**